

FIGURE 1

# MOLECULAR ALTERATIONS IN TUMORS



FUNDAMENTAL TUMOR MOLECULAR DEFECTS  
(MYC, RB, RAS, MSH2, BCL2,...)

IDENTIFY ANALOGOUS DEFECTS IN GENETICALLY  
TRACTABLE ORGANISMS

*S. CEREVISIAE*  
MSH2

*C. ELEGANS*  
GED-9

*D. MELANO-*  
*GASTER*  
MYC

ALTER ANALOGOUS GENE REPRESENTING  
PRIMARY TUMOR DEFECT

PERFORM SYNTHETIC LETHAL SCREEN TO IDENTIFY  
SECONDARY TARGET GENE

*POL-delta*  
*POL-epsilon*

?

DETERMINE ANALOGOUS SECONDARY TARGETS  
IN MAMMALIAN CELLS

DETERMINE  
PHARMACOLOGICAL  
FEASIBILITY

VALIDATE SYNTHETIC  
LETHALITY FOR  
TUMOR CONTEXT

INITIATE CLASSIC TARGET-BASED HIGH-THROUGHPUT  
SCREEN ON VALIDATED SECONDARY TARGET



ANTI-CANCER DRUGS BASED ON TUMOR CONTEXT

# Cell Cycle/DNA Damage Response Pathways

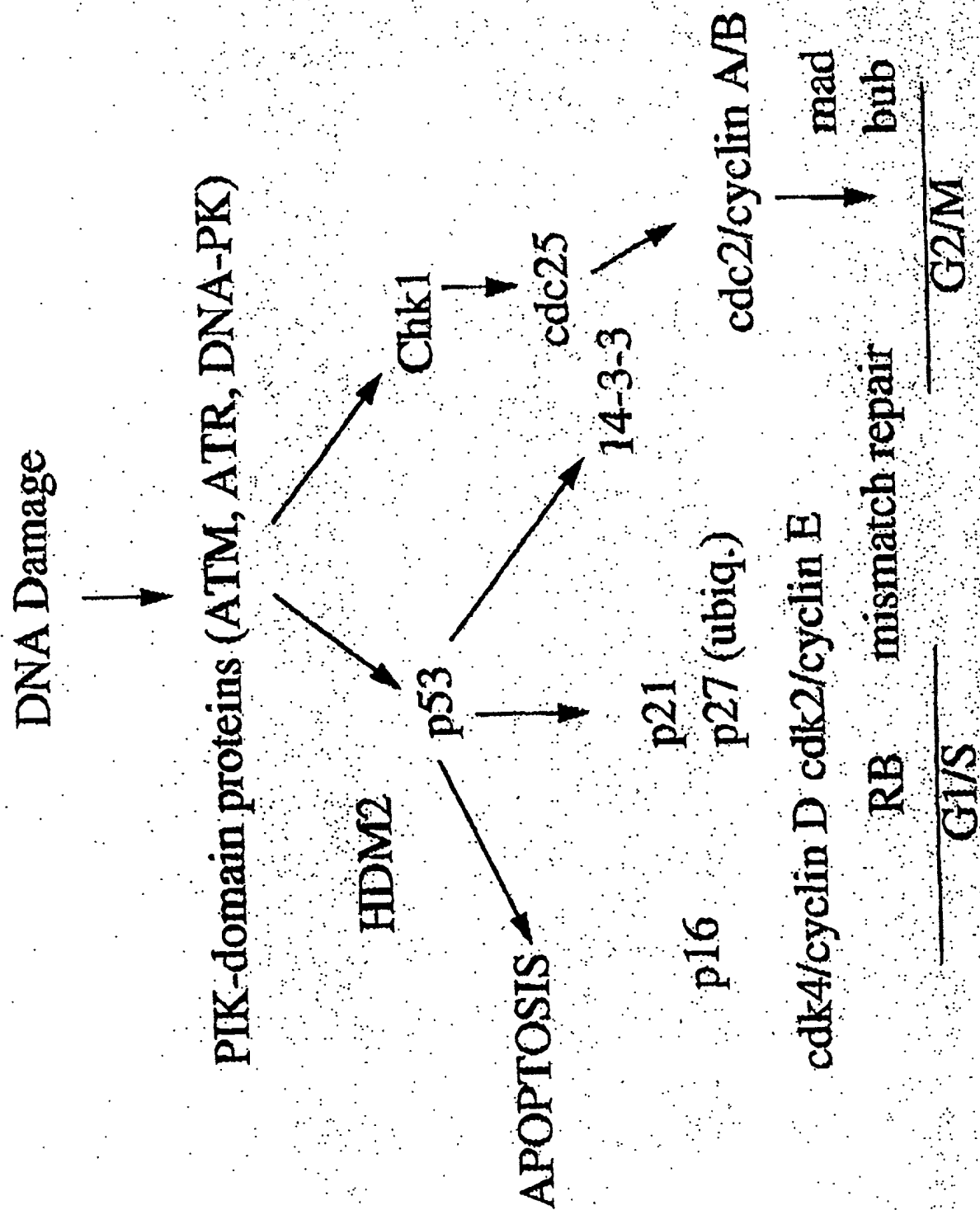


Figure 2

# MAMMALIAN CELL EVALUATION OF ATR AS A TARGET

1. Overexpression of ATR-KD not tolerated in human tumor cell lines (MCF-7, A549)
2. Inducible ATR-KD sensitizes cells to DNA damaging agents
 

MMS (μM)	GM847	GM847/ATRwt(+)	GM847/ATRkd(-)	GM847/ATRkd(+)
0	100	100	100	100
0.2	~80	~80	~80	~50
0.4	~60	~60	~60	~30
0.6	~40	~40	~40	~15
0.8	~20	~20	~20	~8
1.0	~10	~10	~10	~4
1.2	~5	~5	~5	~2
1.4	~2	~2	~2	~1
3. LCK promoter driven ATR-KD transgenic mice have cells stably expressing ATR-KD in thymus

Figure 3

Figure 4

## Synthetic lethality:

- Use primary defect as a selective context to kill tumor cells with an alteration in gene A.
- Combined defects in gene A and gene B kill tumor cells while disrupting gene B activity alone has no effect on normal cells.

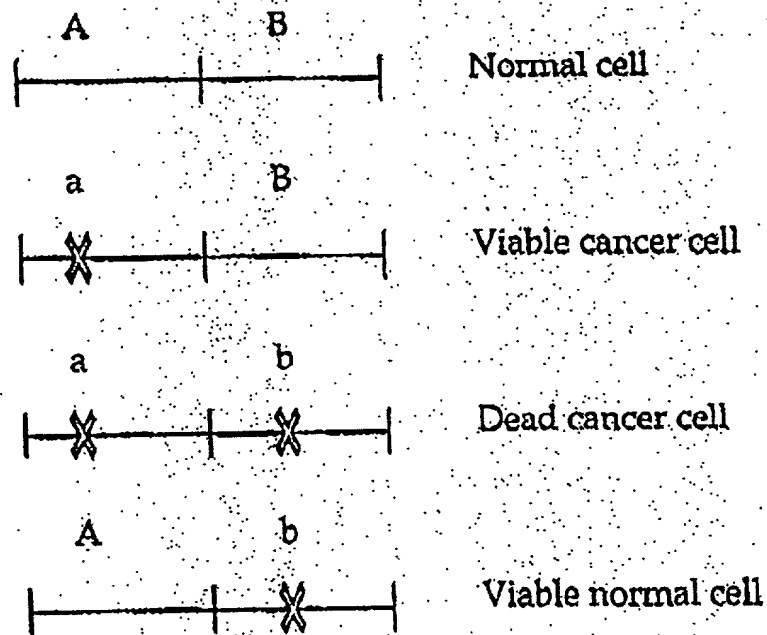


Figure 5

Human genes altered in tumors and their relatives in model genetic systems. Genes that are not structural homologs but act in analogous pathways (such as human p53 and *S. cerevisiae* RAD9) are shown in brackets. *Saccharomyces cerevisiae* genes are designated with superscript Sc, *S. pombe* with Sp, *C. elegans* with Ce, and *D. melanogaster* with Dm. Because of space limitations, this is only a representative list of genes mutated in tumors that have genetic analogs in model systems.

Function	Human genes	Model system analogs: structural homologs or related biological roles
DNA damage checkpoint	p53	[RAD9 <sup>Sc</sup> , rad1 <sup>Sp</sup> ]
	ATM	MEC1 <sup>Sc</sup> , TEL1 <sup>Sc</sup> , rad33 <sup>Sp</sup> , mei-41 <sup>Dm</sup>
DNA mismatch repair	MSH2, MLH1	MSH2 <sup>Sc</sup> , MLH1 <sup>Sc</sup>
Nucleotide excision repair	XP-A, XP-B	RAD14 <sup>Sc</sup> , RAD25 <sup>Sc</sup>
O <sup>6</sup> -methylguanine reversal	MGMT	MGT1 <sup>Sc</sup>
Double-strand break repair	BRCA2, BRCA1	[RAD51 <sup>Sc</sup> , RAD54 <sup>Sc</sup> ]
DNA helicase	BLM	SGS1 <sup>Sc</sup> , rqh1 <sup>Sp</sup>
Growth factor signaling	RAS	RAS1 <sup>Sc</sup> , RAS2 <sup>Sc</sup> , let-60 <sup>Ce</sup>
	NF1	IRA1 <sup>Sc</sup> , IRA2 <sup>Sc</sup>
	MYC	dMyc <sup>Dm</sup>
	PTH	patched <sup>Dm</sup>
Cell cycle control	Cyclin D, Cyclin E	CLN1 <sup>Sc</sup> , CLN2 <sup>Sc</sup> , Cyclin D <sup>Rm</sup> , Cyclin E <sup>Dm</sup>
	P27 <sup>Kip1</sup>	[SIC1 <sup>Sc</sup> ]
	Rb	Rbf <sup>Dm</sup>
Apoptosis	BCL-2	ced-9 <sup>Ce</sup>

# Cell Cycle/DNA Damage Response Pathways

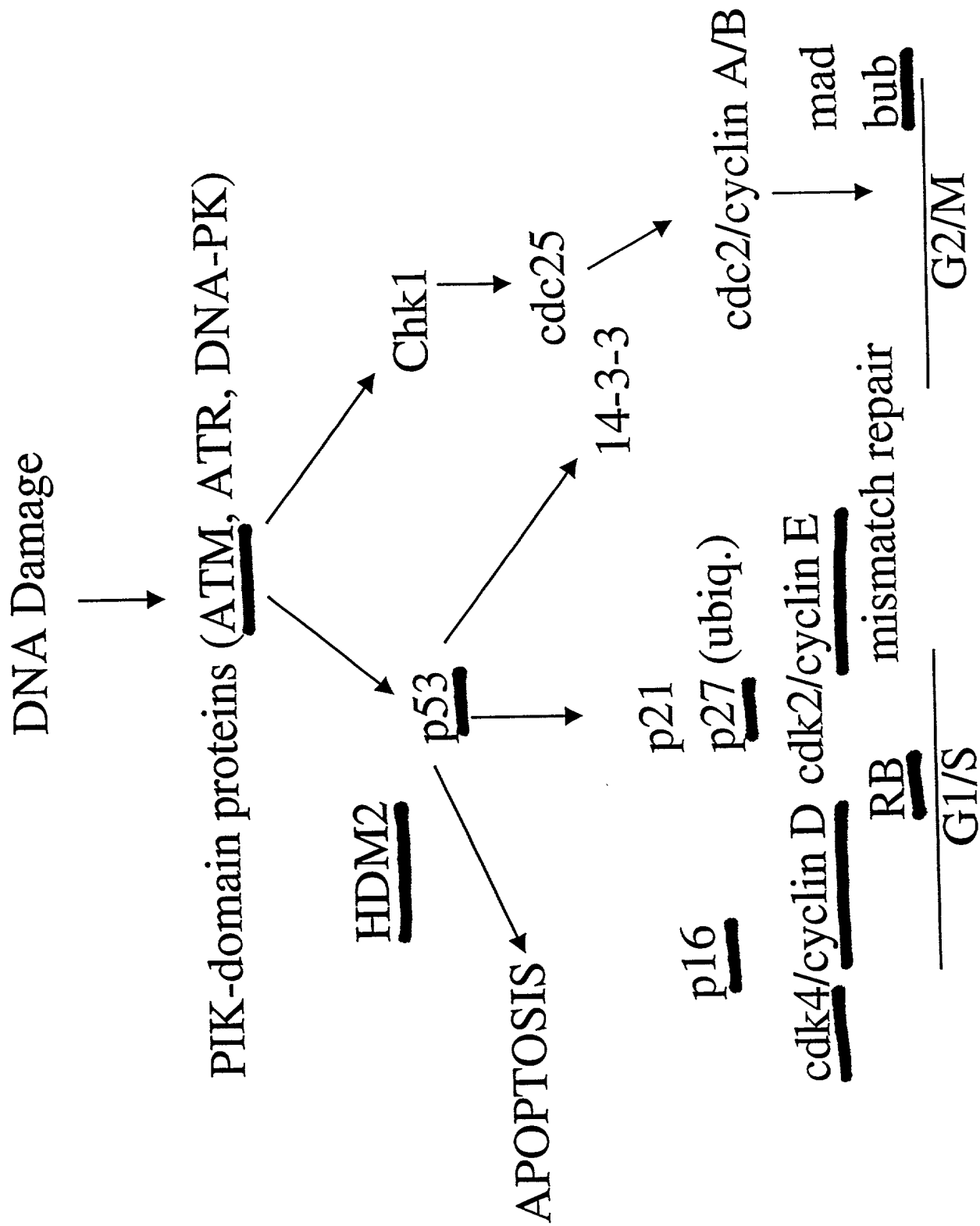


Figure 7

